The pathology of IBD and its modification by liver disease

Roger Feakins
ESP/H-ECCO
# Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2017:

<table>
<thead>
<tr>
<th>Name of the enterprise / Nature of the interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterprise</td>
</tr>
<tr>
<td>None</td>
</tr>
</tbody>
</table>
IBD

- UC
- [IBDU]
- Crohn’s
IBD: distribution of disease

- Ulcerative colitis: continuous
- Crohn’s colitis: discontinuous

Histology: assess distribution of chronic inflammation *and* architectural changes
- between anatomical sites
- between biopsies from the same site
- within biopsies
<table>
<thead>
<tr>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large bowel disease</td>
<td>100%</td>
</tr>
<tr>
<td>Exclusively large bowel</td>
<td>&gt;80%</td>
</tr>
</tbody>
</table>
| Montreal classification | • Rectal  
• Left sided  
• Extensive (including pancolitis) | • Ileal  
• Colonic  
• Ileocolonic  
• Upper GI |
Ileitis

- Favours Crohn’s over UC
- Occurs in 17% UC
  - ? “backwash”
  - ? Ileal UC

Haskell H 2005; Geboes K 1998
Biopsy features of IBD
Features supporting IBD in biopsies (new diagnosis)

- Basal plasmacytosis
- Architectural changes:
  - Crypt distortion
  - Crypt atrophy
  - Irregular / villiform mucosal surface
- Others – less discriminatory:
  - Granulomas (Crohn’s)
  - Paneth cell metaplasia
  - Mucin depletion
Basal plasmacytosis (BPC)

Plasma cells at base of mucosa
+ loss of plasma cell gradient

Value
• earliest histological feature of IBD
• best predictor of IBD

“Crypts with their feet in pools of plasma cells”
Crypt distortion

- Branching
- Loss of parallelism
- Irregularity
- Tortuosity

Crypt atrophy

- Crypt shortening
- Wider crypt spacing
Ulcerative colitis (UC) vs Crohn’s
**UC > Crohn’s (initial biopsies)**

**In any biopsy**
- Diffuse crypt changes
- Diffuse chronic inflammation
- Severe mucin depletion
- No granulomas

**In biopsies from multiple sites**
- Continuous crypt changes
- Absence of ileitis
- Distal > proximal
Typical UC

Diffuse changes within a biopsy

Diffuse changes between biopsies
Crohn’s disease > UC (initial biopsies)

In any biopsy
- Granulomas
- Non-diffuse crypt distortion
- Non-diffuse chronic inflammation

In biopsies from multiple sites
- Anatomical discontinuity
- Ileal inflammation
- Proximal > distal; rectal sparing
Typical Crohn’s disease in biopsies

Discontinuous between sites
Non-diffuse within sites

Granulomas in 20-30%
Ulcerative colitis in resections

Macroscopic
- Continuous
- Sharp cut-off
- Haemorrhagic congested mucosa

Histology
- Diffuse changes
- Mucosa-predominant
- No transmural chronic inflammation
Crohn’s disease in resections

Macroscopic
- Discontinuous / patchy
- More severe proximally
- Ileal disease
- Fat wrapping
- Linear or fissuring ulcers, cobblestoning
- Fibrosis and strictures

Histology
- Transmural chronic inflammation
- Deep fissuring ulcers
- Neural hypertrophy / plexitis
- Fibrosis
## UC vs Crohn’s disease: macroscopic

<table>
<thead>
<tr>
<th>Typical features</th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Continuous</td>
<td>Discontinuous</td>
</tr>
<tr>
<td>Rectal involvement</td>
<td>&gt;95%</td>
<td>50% approx.</td>
</tr>
<tr>
<td>Ileal involvement</td>
<td>&lt; 10%</td>
<td>&gt; 30%</td>
</tr>
<tr>
<td>Sharp border normal to abnormal</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fat wrapping</td>
<td>No</td>
<td>Common</td>
</tr>
<tr>
<td>Fibrosis and strictures</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Inflammatory polyps</td>
<td>Common</td>
<td>Less common; fewer</td>
</tr>
<tr>
<td>Mucosal appearance</td>
<td>Granular, congested, haemorrhagic</td>
<td>Discretely ulcerated; cobblestone; fissuring</td>
</tr>
<tr>
<td>Fistulas</td>
<td>No</td>
<td>Minority</td>
</tr>
</tbody>
</table>

*Loughrey and Shepherd 2017; Feakins and Shepherd 2013*
## UC vs Crohn’s disease: histology

<table>
<thead>
<tr>
<th>Typical features</th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
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<td>50% approx</td>
</tr>
<tr>
<td><strong>Ileal involvement</strong></td>
<td>&lt; 10%</td>
<td>&gt; 30%</td>
</tr>
<tr>
<td><strong>Depth of inflammation</strong></td>
<td>Mucosal</td>
<td>Transmural</td>
</tr>
<tr>
<td><strong>Mucosal architecture</strong></td>
<td>Distorted, extensive changes</td>
<td>Better preserved, focal changes</td>
</tr>
<tr>
<td><strong>Ulcers</strong></td>
<td>Superficial</td>
<td>Linear, fissuring, deep</td>
</tr>
<tr>
<td><strong>Granulomas</strong></td>
<td>Absent / cryptolytic; mucosa only</td>
<td>Mucosal and transmural</td>
</tr>
</tbody>
</table>

_Loughrey and Shepherd 2017; Feakins and Shepherd 2013_
Discontinuity and right sided disease in UC
## Discontinuity in new and longstanding UC

<table>
<thead>
<tr>
<th>Discontinuity</th>
<th>New UC</th>
<th>Longstanding/treated UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caecal patch</td>
<td>5-75%</td>
<td>Common</td>
</tr>
<tr>
<td>Absolute rectal sparing</td>
<td>0-5%</td>
<td>0-44%</td>
</tr>
<tr>
<td>Relative rectal sparing</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Focal or patchy microscopic changes / other discontinuous colonic changes</td>
<td>Uncommon</td>
<td>30-38%</td>
</tr>
</tbody>
</table>
Caecal “patch” in UC

UC around appendix orifice +/- caecum and ascending colon
  • Discontinuous with more distal UC

Histology resembles distal changes

Implications
  • Acceptable in UC
  • Exclude Crohn’s clinically if new disease

Mutinga ML 2004; D’Haens G 1997
Rectal sparing in UC

Rare in new UC in adults

More common in children?

Does not necessarily indicate Crohn’s
but be cautious

In a study with extensive sampling: no absolute rectal sparing in resections


Washington K 2002; Robert ME 2004; Joo M 2010
IBD and PSC
ASSOCIATIONS BETWEEN IBD AND PRIMARY SCLEROSING CHOLANGITIS

IBD can develop PSC

PSC can develop IBD
IBD: how many develop PSC?

- 2-8%
- More likely in UC than in Crohn’s disease
PSC: how many develop IBD?

60-98% in Western Europe / North America

lower in Japan, Singapore

IBD

No IBD
Type of IBD in PSC

- UC 80-95%
- Crohn’s 5-10%
- IBDU rare

*de Vries 2015; Joo M 2009; Boonstra K 2012; Schaeffer DF 2013*
% with each type of PSC-IBD: large series (3402 patients)

<table>
<thead>
<tr>
<th>Condition</th>
<th>% of PSC patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IBD</td>
<td>25.5</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>60.5</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>11.1</td>
</tr>
<tr>
<td>IBD-U</td>
<td>2.9</td>
</tr>
<tr>
<td>Missing</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Alberts R, de Vries EMG 2018
PSC-IBD vs CONVENTIONAL IBD
PSC-IBD vs IBD: severity

Common presentations
• Histological inflammation only
• Significant histological inflammation with minimal endoscopic activity
PSC-UC
PSC-UC vs usual UC

Age at presentation

- Younger in some studies
  - e.g. 24.5 vs 33.5
  - No difference in other studies

Activity

- Endoscopic and histological activity lower

Sano H, Nakazawa T 2011; Schaeffer DF 2013
PSC-UC vs usual UC: distribution

PSC-UC
• ↑ Pancolitis
• ↑ Extensive colitis
• ↓ Left-sided colitis
• ↑↑ “Right-sided UC”
  • Exclusively/predominantly right-sided or more severe on right side
  • Stark contrast with classical UC

<table>
<thead>
<tr>
<th>Pancolitis</th>
<th>Left sided</th>
<th>Right sided</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSC-UC</td>
<td>UC</td>
<td>PSC-UC</td>
<td>UC</td>
</tr>
<tr>
<td>85</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>35</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>55</td>
<td>3</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>83</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If IBD first</td>
<td>If PSC first</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PSC-UC: anatomical pattern vs timing of presentation

- Mild pancolitis if IBD first
- “Right-sided UC” if PSC first
  - PSC first 5%
  - IBD first 74%
  - Both PSC and IBD at presentation 21%

Schaeffer DF Win LL 2013; Sørensen JØ Nielsen OH 2018
PSC-UC: Right-sided UC

Right colon

Left colon
PSC-UC vs. usual UC: rectal sparing and patchiness

Rectal sparing
- Higher rate in some reports
- Other reports: no significant difference
- Rates 6%-66%

Patchy disease proximal to the rectum
- Varies between studies

PSC-UC vs. usual UC: ileitis and pouches

“Backwash” ileitis
- Higher rate in many reports
- 5-43% in PSC-UC
- Difference not significant in one report

Pouch outcomes
- Pouchitis more common?
- Pouch failure probably similar

Histology of PSC-UC vs. usual UC

- Basal plasmacytosis focal
- Crypt changes and mucin depletion often mild

Risks misdiagnosis as Crohn’s or IBDU

Schaeffer DF Win LL 2013
# PSC-UC vs. usual UC: eosinophil activation

<table>
<thead>
<tr>
<th></th>
<th>PSC-UC</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic eosinophils</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Expression of eosinophil activation markers</td>
<td>No increase</td>
<td>↑</td>
</tr>
<tr>
<td>Colonic level of pro-inflammatory cytokines</td>
<td>No increase</td>
<td>↑ (in active disease)</td>
</tr>
</tbody>
</table>

Lampinen M 2018
Intestinal microbiota in PSC-UC and UC

Nominally significant differences for multiple microbial genera

But results are not robust

No strong consistent PSC-specific microbial associations in UC

Kevans D 2016
PSC-Crohn’s disease

Limited data
PSC Crohn’s disease vs usual Crohn’s: limited data

<table>
<thead>
<tr>
<th>Condition</th>
<th>PSC-Crohn’s vs usual Crohn’s</th>
<th>PSC-Crohn’s (approx.)</th>
<th>Usual Crohn’s (approx.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic involvement</td>
<td>↑/=</td>
<td>&gt;90% - 100%</td>
<td>60%</td>
</tr>
<tr>
<td>Isolated colitis</td>
<td>↑/=</td>
<td>37-82%</td>
<td>30-40%</td>
</tr>
<tr>
<td>Extensive colitis</td>
<td>↑/=</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated ileal disease</td>
<td>↓↓</td>
<td>0-6%</td>
<td>30%</td>
</tr>
<tr>
<td>Right-sided continuous colitis with patchy left-sided colitis</td>
<td></td>
<td>9/43</td>
<td></td>
</tr>
</tbody>
</table>
# PSC Crohn’s disease vs usual Crohn’s disease

<table>
<thead>
<tr>
<th></th>
<th>PSC-Crohn’s vs usual Crohn’s</th>
<th>PSC-Crohn’s</th>
<th>Usual Crohn’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strictures</td>
<td>↓/=</td>
<td>7%</td>
<td>30%</td>
</tr>
<tr>
<td>Severe penetrating disease</td>
<td>↓/=</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stricturing/penetrating</td>
<td>=</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Activity</td>
<td>/=↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perianal fistulas</td>
<td>↓</td>
<td>3%</td>
<td>33%</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>=</td>
<td>22%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Lindstrom JS 2011; Halliday JS 2012; O’Toole A 2012; Navaneethan U 2016
Paediatric PSC-IBD
Paediatric PSC-IBD vs IBD: similar to adults

Types

- 89% UC
- 11% Crohn's disease

Distribution

- Pancolitis more likely in UC-PSC than in non-PSC UC
- Rectal sparing in UC: conflicting data

Crohn’s disease

- ↓↓ Perianal disease, fistulas, strictures

Pouchitis

- Common

IgG4 disease

- Raised serum IgG4
- High tissue ratio of IgG4+ to IgG+ plasma cells
- Typical histology – phlebitis, storiform fibrosis etc

Presentations
- Type 1 autoimmune pancreatitis (AIP) 60%
- IgG4-related sclerosing cholangitis 20%-88%: not PSC

Gidwaney NG, Pawa S 2017; Bledsoe JR, Della-Torre E 2018
### IgG4+ plasma cells in IBD and PSC-UC

<table>
<thead>
<tr>
<th></th>
<th>UC active</th>
<th>UC inactive</th>
<th>PSC + active colitis</th>
<th>PSC + inactive colitis</th>
<th>Crohn’s</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion with high mucosal IgG4+ plasma cells</td>
<td>30%</td>
<td>few</td>
<td>64%</td>
<td>25%</td>
<td>few</td>
<td>few</td>
</tr>
</tbody>
</table>

- Not always simple, e.g. moderate/severe IgG4+ lymphoplasmacytic infiltrate in 25% PSC liver explants
- PSC and IBD are not IgG4-related diseases

Raina A, Yadav D 2013; Zhang L 2010; Fischer S 2014
Unexplained cholangitis: value of colorectal assessment

Evidence for PSC

• Presence of IBD
• Unusual characteristics of IBD e.g. right-sided UC

<table>
<thead>
<tr>
<th>Percentage with IBD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG4-SC</td>
<td>PSC</td>
</tr>
<tr>
<td>0%</td>
<td>62.5%</td>
</tr>
<tr>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>6%</td>
<td>70%</td>
</tr>
<tr>
<td>6%</td>
<td>68%</td>
</tr>
</tbody>
</table>

Table modified from: Nakazawa T, Naitoh I et al 2014
Autoimmune sclerosing cholangitis (AISC)

**Distinctive disease entity?**

**Overlap with PSC and autoimmune hepatitis**

**Colon**

- 18/23 right sided UC-like colitis, often with rectal sparing
- Microscopic changes often mild

Floreani 2005; Bjarnason; Gregorio 2001; Bogdanos 2008
CRC in PSC-IBD compared to usual IBD

- Higher risk?
- Faster progression of dysplasia?
- Younger age of onset?
- Proportionately more right sided neoplasia?
- Studies conflict

Brackmann S, Andersen SN 2009; de Vries 2015
Summary: IBD

### IBD vs non-IBD
- Basal plasmacytosis
- Architectural changes

### UC > Crohn’s
- Diffuse continuous mucosal disease
- No ileal disease
- Distal > proximal

### Crohn’s disease > UC
- Granulomas – if present
- Transmural
- Ileal disease
- Proximal > distal
Summary: PSC-IBD

IBD may occur before, after, or with the diagnosis of PSC

**IBD first**
- 2-8% develop PSC

**PSC first**
- 60-90% develop IBD

**Type of IBD in PSC**
- UC > 85%
- Crohn’s < 15%
- IBDU rare
Summary: PSC-UC vs conventional UC

Distribution

- ↑ Pancolitis; typically if IBD presents before PSC
- ↑ Right-sided UC; typically if PSC presents before IBD

Inconsistent differences

- ↑ Rectal sparing
- ↑ “Backwash” ileitis
- ↑ Rates of dysplasia and risk of malignancy

Other differences

- ↓ Clinical activity
- ↓ Histological activity
- Chronic histological changes less severe
Summary: PSC-Crohn’s vs conventional Crohn’s

**Limited information**

**Consistent difference**

- ↓ Isolated ileitis

**Inconsistent differences**

- ↑ Colonic involvement
- ↑ Isolated Crohn’s colitis
- ↓ Fistulas, strictures and penetrating disease
Summary: practical points

Remember the association between PSC and IBD

- When assessing liver biopsies from IBD patients
- When assessing GI samples from PSC patients
- If IBD seems atypical or oddly distributed

Be aware of “right-sided UC”

- Clinicians may be confused
- Avoid over-diagnosing Crohn’s disease

If there is unexplained bile duct disease

- Presence of IBD and features of IBD may support a diagnosis of PSC
Histology completes the picture

- Imaging
- Endoscopy
- Symptoms
- Past history
- Histology